

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20297/S004

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20297/S004

Trade Name: Coreg 3.125, 6.25, 12.5 and 25 mg Tablets

Generic Name: (carvedilol)

Sponsor: SmithKline Beecham Pharmaceuticals

Approval Date: September 8, 1999

INDICATION: Provides for final printed labeling revised under the Precautions/Drug Interactions section to describe the effects of carvedilol on cyclosporin concentrations in renal transplant patients.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20297/S004

APPROVAL LETTER



Food and Drug Administration
Rockville MD 20857

NDA 20-297/S-004

SEP 8 1999

SmithKline Beecham Pharmaceuticals
Attention: Ms. Catherine K. Clark
1250 S. Collegeville Road, UP4455
P.O. Box 5089
Collegeville, PA 19426-0989

Dear Ms. Clark:

Please refer to your supplemental new drug application dated May 6, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coreg (carvedilol) 3.125, 6.25, 12.5 and 25 mg Tablets.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

This supplemental new drug application provides for final printed labeling revised under the Precautions/Drug Interactions section to describe the effects of carvedilol on cyclosporin concentrations in renal transplant patients. The following section was added:

Cyclosporin: Modest increases in mean trough cyclosporin concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30% of patients, the dose of cyclosporin had to be reduced in order to maintain cyclosporin concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclosporin was reduced about 20% in these patients. Due to wide interindividual variability in the dose adjustment required, it is recommended that cyclosporin concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporin be adjusted as appropriate.

Also added to the **How Supplied** section was the statement, "Rx only" as well as minor editorial changes.

Your submission stated May 4, 1999 as the implementation date for this change.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling included with your May 6, 1999 submission. Accordingly, the supplemental application is approved effective on the date of this.

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We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Zelda McDonald
Regulatory Health Project Manager
(301)594-5300

Sincerely,

JS/9/8/96

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20297/S004

FINAL PRINTED LABELING

APPROVED

Labeling: ORIGINALNDA No: 20-297 Rc'd. 5-7-99Reviewed by: [Signature]
8/19/99

CO:LSA



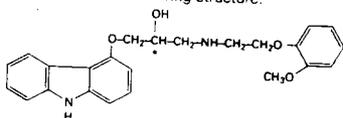
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PRESCRIBING INFORMATION

COREG[®]brand of
**carvedilol
Tablets****DESCRIPTION**

Carvedilol is a nonselective β -adrenergic blocking agent with α_1 -blocking activity. It is (±)-1-(Carbazol-4-yloxy)-3-[(2-lo-methoxyphenoxy)ethyl]amino-2-propanol. It is a racemic mixture with the following structure:



carvedilol

Tablets for Oral Administration:

Coreg (carvedilol) is a white, oval, film-coated tablet containing 3.125 mg, 6.25 mg, 12.5 mg or 25 mg of carvedilol. The 6.25 mg, 12.5 mg and 25 mg tablets are Tiltab[®] tablets. Inactive ingredients consist of colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, sucrose and titanium dioxide.

Carvedilol is a white to off-white powder with a molecular weight of 406.5 and a molecular formula of $C_{24}H_{26}N_2O_4$. It is freely soluble in dimethylsulfoxide; soluble in methylene chloride and methanol; sparingly soluble in ethyl ether; and practically insoluble in water, gastric fluid (simulated, TS, pH 1.1) and intestinal fluid (simulated, TS without pectin, pH 7.5).

CLINICAL PHARMACOLOGY

Coreg is a racemic mixture in which nonselective β -adrenoreceptor blocking activity is present in the S(-) enantiomer and α -adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency. Coreg has no intrinsic sympathomimetic activity.

Pharmacokinetics

Coreg is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25% to 35% due to a significant degree of first-pass metabolism. Following oral administration, the apparent mean terminal elimination half-life of carvedilol generally ranges from 7 to 10 hours. Plasma concentrations achieved are proportional to the oral dose administered. When administered with food, the rate of absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability. Taking Coreg with food should minimize the risk of orthostatic hypotension.

Carvedilol is extensively metabolized. Following oral administration of radiolabelled carvedilol to healthy volunteers, carvedilol accounted for only about 7% of the total radioactivity in plasma as measured by area under the curve (AUC). Less than 2% of the dose was excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation with glucuronidation and sulfation. The metabolites of carvedilol

are excreted primarily via the bile into the feces. Demethylation and hydroxylation at the phenol ring produce three active metabolites with β -receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol for β -blockade.

Compared to carvedilol, the three active metabolites exhibit weak vasodilating activity. Plasma concentrations of the active metabolites are about one-tenth of those observed for carvedilol and have pharmacokinetics similar to the parent.

Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R(+)-carvedilol approximately 2 to 3 times higher than S(-)-carvedilol following oral administration in healthy subjects. The mean apparent terminal elimination half-lives for R(+)-carvedilol range from 5 to 9 hours compared with 7 to 11 hours for the S(-)-enantiomer.

The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and 5'-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be of primary importance in the O-methylation pathway of S(-)-carvedilol.

Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared to extensive metabolizers. In contrast, plasma levels of S(-)-carvedilol are increased only about 20% to 25% in poor metabolizers, indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol. The pharmacokinetics of carvedilol do not appear to be different in poor metabolizers of S-mephenytoin (patients deficient in cytochrome P450 2C19).

Carvedilol is more than 98% bound to plasma proteins, primarily with albumin. The plasma-protein binding is independent of concentration over the therapeutic range. Carvedilol is a basic, lipophilic compound with a steady-state volume of distribution of approximately 115 L, indicating substantial distribution into extravascular tissues. Plasma clearance ranges from 500 to 700 mL/min.

Congestive Heart Failure: Steady-state plasma concentrations of carvedilol and its enantiomers increased proportionally over the 6.25 to 50 mg dose range in patients with congestive heart failure. Compared to healthy subjects, congestive heart failure patients had increased mean AUC and C_{max} values for carvedilol and its enantiomers, with up to 50% to 100% higher values observed in 6 patients with NYHA class IV heart failure. The mean apparent terminal elimination half-life for carvedilol was similar to that observed in healthy subjects.

Pharmacokinetic Drug-Drug Interactions: Since carvedilol undergoes substantial oxidative metabolism, the metabolism and pharmacokinetics of carvedilol may be affected by induction or inhibition of cytochrome P450 enzymes.

Rifampin: In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin (600 mg daily for 12 days) decreased the AUC and C_{max} of carvedilol by about 70%.

Cimetidine: In a pharmacokinetic study conducted in 10 healthy male subjects, cimetidine (1000 mg/day) increased the steady-state AUC of carvedilol by 30% with no change in C_{max} .

Glyburide: In 12 healthy subjects, combined administration of carvedilol (25 mg once daily) and a single dose of glyburide did not result in a clinically relevant pharmacokinetic interaction for either compound.

Hydrochlorothiazide: A single oral dose of carvedilol 25 mg did not alter the pharmacokinetics of a single oral dose of hydrochlorothiazide 25 mg in 12 patients with hypertension. Likewise, hydrochlorothiazide had no effect on the pharmacokinetics of carvedilol.

Digoxin: Following concomitant administration of carvedilol (25 mg once daily) and digoxin (0.25 mg once daily) for 14 days, steady-state AUC and trough concentrations of digoxin were increased by 14% and 16%, respectively, in 12 hypertensive patients.

Torsemide: In a study of 12 healthy subjects, combined oral administration of carvedilol 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant differences in their pharmacokinetics compared with administration of the drugs alone.

Warfarin: Carvedilol (12.5 mg twice daily) did not have an effect on the steady-state prothrombin time ratios and did not alter the pharmacokinetics of R(+) and S(-)-warfarin following concomitant administration with warfarin in 9 healthy volunteers.

Special Populations

Elderly: Plasma levels of carvedilol average about 50% higher in the elderly compared to young subjects.

Hepatic Impairment: Compared to healthy subjects, patients with cirrhotic liver disease exhibit significantly higher concentrations of carvedilol (approximately 4- to 7-fold) following single-dose therapy (see WARNINGS, Hepatic Injury).

Renal Insufficiency: Although carvedilol is metabolized primarily by the liver, plasma concentrations of carvedilol have been reported to be increased in patients with renal impairment. Based on mean AUC data, approximately 40% to 50% higher plasma concentrations of carvedilol were observed in hypertensive patients with moderate to severe renal impairment compared to a control group of hypertensive patients with normal renal function. However, the ranges of AUC values were similar for both groups. Changes in mean peak plasma levels were less pronounced, approximately 12% to 26% higher in patients with impaired renal function.

Consistent with its high degree of plasma protein-binding, carvedilol does not appear to be cleared significantly by hemodialysis.

Pharmacodynamics and Clinical Trials**Congestive Heart Failure****Pharmacodynamics**

The basis for the beneficial effects of Coreg (carvedilol) in congestive heart failure is not established.

Two placebo-controlled studies compared the acute hemodynamic effects of Coreg to baseline measurements in 59 and 49 patients with NYHA class II-IV heart failure receiving diuretics, ACE inhibitors, and digitalis. There were significant reductions in systemic blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and heart rate. Initial effects on cardiac output, stroke volume index, and systemic vascular resistance were small and variable.

These studies measured hemodynamic effects again at 12 to 14 weeks. Coreg significantly reduced systemic blood pressure, pulmonary artery pressure, right atrial pressure, systemic vascular resistance, and heart rate, while stroke volume index was increased.

Among 839 patients with NYHA class III-IV heart failure treated for 26 to 52 weeks in 4 U.S. placebo-controlled trials, average left ventricular ejection fraction (EF) measured by radionuclide ventriculography increased by 8 EF units (%) in Coreg patients and by 2 EF units in placebo patients (between-group difference of 6 EF units). This treatment effect was nominally statistically significant in each trial.

Hypertension**Pharmacodynamics**

The mechanism by which β -blockade produces an antihypertensive effect has not been established.

β -adrenoreceptor blocking activity has been demonstrated in animal and human studies showing that carvedilol (1) reduces cardiac output in normal subjects; (2) reduces exercise- and/or isoproterenol-induced tachycardia and (3) reduces reflex orthostatic tachycardia. Significant β -adrenoreceptor blocking effect is usually seen within 1 hour of drug administration.

α_1 -adrenoreceptor blocking activity has been demonstrated in human and animal studies, showing that carvedilol (1) attenuates the pressor effects of phenylephrine; (2) causes vasodilation and (3) reduces peripheral vascular resistance. These effects contribute to the reduction of blood pressure and usually are seen within 30 minutes of drug administration.

Due to the α_1 -receptor blocking activity of carvedilol, blood pressure is lowered more in the standing than in the supine position, and symptoms of postural hypotension (1.8%), including rare instances of syncope, can occur.

Following oral administration, when postural hypotension has occurred, it has been transient and is uncommon when Coreg (carvedilol) is administered with food at the recommended starting dose and titration increments are closely followed (see DOSAGE AND ADMINISTRATION).

In hypertensive patients with normal renal function, therapeutic doses of Coreg decreased renal vascular resistance with no change in glomerular filtration rate or renal plasma flow. Changes in excretion of sodium, potassium, uric acid and phosphorus in hypertensive patients with normal renal function were similar after Coreg and placebo.

Coreg has little effect on plasma catecholamines, plasma aldosterone or electrolyte levels, but it does significantly reduce plasma renin activity when given for at least 4 weeks. It also increases levels of atrial natriuretic peptide.

CLINICAL TRIALS

Congestive Heart Failure

Four U.S. multicenter, double-blind, placebo-controlled studies enrolled 1094 patients (696 randomized to carvedilol) with NYHA class II-III heart failure and ejection fraction <0.35. The vast majority were on digitalis, diuretics, and an ACE inhibitor at study entry. Patients were assigned to the studies based upon exercise ability. An Australia-New Zealand double-blind, placebo-controlled study enrolled 415 patients (half randomized to carvedilol) with less severe heart failure. All protocols excluded patients expected to undergo cardiac surgery during the 6 to 12 months of double-blind follow-up. All randomized patients had tolerated a 2-week course on carvedilol 6.25 mg b.i.d.

In each study, there was a primary end-point, either progression of heart failure (one U.S. study) or exercise tolerance (2 U.S. studies meeting enrollment goals and the Australia-New Zealand study). There were many secondary end-points specified in these studies, including NYHA classification, patient and physician global assessments, and cardiovascular hospitalization. Death was not a specified end-point in any study, but it was analyzed in all studies. Other analyses not prospectively planned included the sum of deaths and total cardiovascular hospitalizations. In situations where the primary end-points of a trial do not show a significant benefit of treatment, assignment of significance values to the other results is complex, and such values need to be interpreted cautiously.

The results of the U.S. and Australia-New Zealand trials were as follows:

Slowing Progression of Heart Failure: One U.S. multicenter study (366 subjects) had as its primary end-point the sum of cardiovascular mortality, cardiovascular hospitalization, and sustained increase in heart failure medications. Heart failure progression was reduced during an average follow-up of 7 months, by 48% ($p=0.008$).

In the Australia-New Zealand study, death and total hospitalizations were reduced by about 25% over 18 to 24 months. In the three largest U.S. studies, death and total hospitalizations were reduced by 19%, 39% and 49%, nominally statistically significant in the last two studies. The Australia-New Zealand results were statistically borderline.

Functional Measures: None of the multicenter studies had NYHA classification as a primary end-point, but all such studies had it as a secondary end-point. There was at least a trend toward improvement in NYHA class in all studies. Exercise tolerance was the primary end-point in 3 studies; in none was a statistically significant effect found.

Subjective Measures: Quality of life, as measured with a standard questionnaire (a primary end-point in one study), was unaffected by carvedilol. However, patients' and investigators' global assessments showed significant improvement in most studies.

Mortality: Mortality was not a planned end-point in any study. Overall, in the U.S. trials, mortality was reduced, nominally significantly so in 2 studies, but the actual effect size and statistical significance of this observation are difficult to define.

Hypertension

Coreg was studied in two placebo-controlled trials that utilized twice-daily dosing, at total daily doses of 12.5 to 50 mg. In these and other studies, the starting dose did not exceed 12.5 mg. At 50 mg per day, Coreg reduced sitting trough (12-hour) blood pressure by about 9/5.5 mm Hg; at 25 mg/day the effect was about 7.5/3.5 mm Hg. Comparisons of trough to peak blood pressure response showed a trough to peak ratio for blood pressure response of about 65%. Heart rate fell by about 7.5 beats per minute at 50 mg/day.

In general, as is true for other β -blockers, responses were smaller in black than non-black patients. There were no age- or gender-related differences in response.

The peak antihypertensive effect occurred 1 to 2 hours after a dose. The dose-related blood pressure response was accompanied by a dose-related increase in adverse effects (see ADVERSE REACTIONS).

INDICATIONS AND USAGE

Congestive Heart Failure

Coreg is indicated for the treatment of mild or moderate (NYHA class II or III) heart failure of ischemic or cardiomyopathic origin, in conjunction with digitalis, diuretics, and ACE inhibitor, to reduce the progression of disease as evidenced by cardiovascular death, cardiovascular hospitalization, or the need to adjust other heart failure medications.

Coreg may be used in patients unable to tolerate an ACE inhibitor. Coreg may be used in patients who are or are not receiving digitalis, hydralazine or nitrate therapy.

Hypertension

Coreg (carvedilol) is also indicated for the management of essential hypertension. It can be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics (see PRECAUTIONS, Drug Interactions).

CONTRAINDICATIONS

Coreg is contraindicated in patients with NYHA class IV decompensated cardiac failure requiring intravenous inotropic therapy, bronchial asthma (two cases of death from status asthmaticus have been reported in patients receiving single doses of Coreg) or related bronchospastic conditions, second- or third-degree AV block, sick sinus syndrome (unless a permanent pacemaker is in place), cardiogenic shock or severe bradycardia.

Use of Coreg in patients with clinically manifest hepatic impairment is not recommended.

Coreg is contraindicated in patients with hypersensitivity to the drug.

WARNINGS

Hepatic Injury: Mild hepatocellular injury, confirmed by rechallenge, has occurred rarely with Coreg therapy. In controlled studies of hypertensive patients, the incidence of liver function abnormalities reported as adverse experiences was 1.1% (13 of 1,142 patients) in patients receiving Coreg and 0.9% (4 of 462 patients) in those receiving placebo. One patient receiving carvedilol in a placebo-controlled trial withdrew for abnormal hepatic function.

In controlled studies of congestive heart failure, the incidence of liver function abnormalities reported as adverse experiences was 5.0% (38 of 765 patients) in patients receiving Coreg and 4.6% (20 of 437 patients) in those receiving placebo. Three patients receiving carvedilol (0.4%) and two patients receiving placebo (0.5%) in placebo-controlled trials withdrew for abnormal hepatic function.

Hepatic injury has been reversible and has occurred after short- and/or long-term therapy with minimal clinical symptomatology. No deaths due to liver function abnormalities have been reported.

At the first symptom/sign of liver dysfunction (e.g., pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness or unexplained "flu-like" symptoms), laboratory testing should be performed. If the patient has laboratory evidence of liver injury or jaundice, carvedilol should be stopped and not restarted.

Peripheral Vascular Disease: β -blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

Anesthesia and Major Surgery: If Coreg treatment is to be continued perioperatively, particular care should be taken when anesthetic agents which depress myocardial function, such as ether, cyclopropane and trichloroethylene, are used. See OVERDOSAGE for information on treatment of bradycardia and hypotension.

Diabetes and Hypoglycemia: β -blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective β -blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned about these possibilities and carvedilol should be used with caution. In congestive heart failure patients, there is a risk of worsening hyperglycemia (see PRECAUTIONS).

Thyrotoxicosis: β -adrenergic blockade may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt

withdrawal of β -blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate thyroid storm.

PRECAUTIONS

General

Since Coreg (carvedilol) has β -blocking activity, it should not be discontinued abruptly, particularly in patients with ischemic heart disease. Instead, it should be discontinued over 1 to 2 weeks.

In clinical trials, Coreg caused bradycardia in about 2% of hypertensive patients and 9% of congestive heart failure patients. If pulse rate drops below 55 beats/min., the dosage should be reduced.

Hypotension and postural hypotension occurred in 9.7% and syncope in 3.4% of congestive heart failure patients receiving carvedilol compared to 3.6% and 2.5% of placebo patients, respectively. The risk for these events was highest during the first 30 days of dosing, corresponding to the up-titration period and was a cause for discontinuation of therapy in 0.7% of carvedilol patients, compared to 0.4% of placebo patients.

Postural hypotension occurred in 1.8% and syncope in 0.1% of hypertensive patients, primarily following the initial dose or at the time of dose increase and was a cause for discontinuation of therapy in 1% of patients.

To decrease the likelihood of syncope or excessive hypotension, treatment should be initiated with 3.125 mg b.i.d. for congestive heart failure patients and 6.25 mg b.i.d. for hypertensive patients. Dosage should then be increased slowly, according to recommendations in the DOSAGE AND ADMINISTRATION section, and the drug should be taken with food. During initiation of therapy, the patient should be cautioned to avoid situations such as driving or hazardous tasks, where injury could result should syncope occur.

Rarely, use of carvedilol in patients with congestive heart failure has resulted in deterioration of renal function. Patients at risk appear to be those with low blood pressure (systolic BP <100 mm Hg), ischemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency. Renal function has returned to baseline when carvedilol was stopped. In patients with these risk factors it is recommended that renal function be monitored during up-titration of carvedilol and the drug discontinued or dosage reduced if worsening of renal function occurs.

Worsening cardiac failure or fluid retention may occur during up-titration of carvedilol. If such symptoms occur, diuretics should be increased and the carvedilol dose should not be advanced until clinical stability resumes (see DOSAGE AND ADMINISTRATION). Occasionally it is necessary to lower the carvedilol dose or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of carvedilol.

In patients with pheochromocytoma, an α -blocking agent should be initiated prior to the use of any β -blocking agent. Although carvedilol has both α - and β -blocking pharmacologic activities, there has been no experience with its use in this condition. Therefore, caution should be taken in the administration of carvedilol to patients suspected of having pheochromocytoma.

Agents with non-selective β -blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There has been no clinical experience with carvedilol in these patients although the α -blocking activity may prevent such symptoms. However, caution should be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

Risk of Anaphylactic Reaction

While taking β -blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema)

Patients with bronchospastic disease should, in general, not receive β -blockers. Coreg may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if Coreg (carvedilol) is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous β -agonists is minimized.

In clinical trials of patients with congestive heart failure, patients with bronchospastic disease were enrolled if they did not require oral or inhaled medication to treat their bronchospastic disease. In such patients, it is rec-

ommended that carvedilol be used with caution. The dosing recommendations should be followed closely and the dose should be lowered if any evidence of bronchospasm is observed during up-titration.

Hypertensive Patients with Left Ventricular Failure: In hypertensive patients who have congestive heart failure controlled with digitalis, diuretics and/or an angiotensin-converting enzyme inhibitor, Coreg (carvedilol) may be used. However, since it is likely that such patients are dependent, in part, on sympathetic stimulation for circulatory support, it is recommended that dosing follow the instructions for patients with congestive heart failure.

In congestive heart failure patients with diabetes, carvedilol therapy may lead to worsening hyperglycemia, which responds to intensification of hypoglycemic therapy. It is recommended that blood glucose be monitored when carvedilol dosing is initiated, adjusted, or discontinued.

Information for Patients

Patients taking Coreg should be advised of the following:

- they should not interrupt or discontinue using Coreg without a physician's advice.

- congestive heart failure patients should consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath.

- they may experience a drop in blood pressure when standing, resulting in dizziness and, rarely, fainting. Patients should sit or lie down when these symptoms of lowered blood pressure occur.

- if patients experience dizziness or fatigue, they should avoid driving or hazardous tasks.

- they should consult a physician if they experience dizziness or faintness, in case the dosage should be adjusted.

- they should take Coreg with food.

- diabetic patients should report any changes in blood sugar levels to their physician.

- contact lens wearers may experience decreased lacrimation.

Drug Interactions

(Also see CLINICAL PHARMACOLOGY, Pharmacokinetic Drug-Drug Interactions.)

Inhibitors of CYP2D6; poor metabolizers of debrisoquin: Interactions of carvedilol with strong inhibitors of CYP2D6 (such as quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would be expected to increase blood levels of the R(+) enantiomer of carvedilol (see CLINICAL PHARMACOLOGY). Retrospective analysis of side effects in clinical trials showed that poor 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the α -blocking R(+) enantiomer.

Catecholamine-depleting agents: Patients taking both agents with β -blocking properties and a drug that can deplete catecholamines (e.g., reserpine and monoamine oxidase inhibitors) should be observed closely for signs of hypotension and/or severe bradycardia.

Clonidine: Concomitant administration of clonidine with agents with β -blocking properties may potentiate blood-pressure- and heart-rate-lowering effects. When concomitant treatment with agents with β -blocking properties and clonidine is to be terminated, the β -blocking agent should be discontinued first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage.

Cyclosporin: Modest increases in mean trough cyclosporin concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30% of patients, the dose of cyclosporin had to be reduced in order to maintain cyclosporin concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclosporin was reduced about 20% in these patients. Due to wide inter-individual variability in the dose adjustment required, it is recommended that cyclosporin concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporin be adjusted as appropriate.

Digoxin: Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Both digoxin and Coreg slow AV conduction. Therefore, increased monitoring of digoxin is recommended when initiating, adjusting or discontinuing Coreg.

Inducers and inhibitors of hepatic metabolism: Ritampin reduced plasma concentrations of carvedilol by about

70%. Cimetidine increased AUC by about 30% but caused no change in C_{max} .

Calcium channel blockers: Isolated cases of conduction disturbance (rarely with hemodynamic compromise) have been observed when Coreg is co-administered with diltiazem. As with other agents with β -blocking properties, if Coreg (carvedilol) is to be administered orally with calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.

Insulin or oral hypoglycemics: Agents with β -blocking properties may enhance the blood-sugar-reducing effect of insulin and oral hypoglycemics. Therefore, in patients taking insulin or oral hypoglycemics, regular monitoring of blood glucose is recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility In 2-year studies conducted in rats given carvedilol at doses up to 75 mg/kg/day (12 times the maximum recommended human dose [MRHD] when compared on a mg/m² basis) or in mice given up to 200 mg/kg/day (16 times the MRHD on a mg/m² basis), carvedilol had no carcinogenic effect.

Carvedilol was negative when tested in a battery of genotoxicity assays, including the Ames and the CHO/HGPRT assays for mutagenicity and the *in vitro* hamster micronucleus and *in vivo* human lymphocyte cell tests for clastogenicity.

At doses ≥ 200 mg/kg/day (≥ 32 times the MRHD as mg/m²) carvedilol was toxic to adult rats (sedation, reduced weight gain) and was associated with a reduced number of successful matings, prolonged mating time, significantly fewer corpora lutea and implants per dam and complete resorption of 18% of the litters. The no-observed-effect dose level for overt toxicity and impairment of fertility was 60 mg/kg/day (10 times the MRHD as mg/m²).

Pregnancy: Teratogenic Effects. Pregnancy Category C. Studies performed in pregnant rats and rabbits given carvedilol revealed increased post-implantation loss in rats at doses of 300 mg/kg/day (50 times the MRHD as mg/m²) and in rabbits at doses of 75 mg/kg/day (25 times the MRHD as mg/m²). In the rats, there was also a decrease in fetal body weight at the maternally toxic dose of 300 mg/kg/day (50 times the MRHD as mg/m²), which was accompanied by an elevation in the frequency of fetuses with delayed skeletal development (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was 60 mg/kg/day (10 times the MRHD as mg/m²); in rabbits it was 15 mg/kg/day (5 times the MRHD as mg/m²). There are no adequate and well-controlled studies in pregnant women. Coreg should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Studies in rats have shown that carvedilol and/or its metabolites (as well as other β -blockers) cross the placental barrier and are excreted in breast milk. There was increased mortality at one week post-partum in neonates from rats treated with 60 mg/kg/day (10 times the MRHD as mg/m²) and above during the last trimester through day 22 of lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from β -blockers, especially bradycardia, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. The effects of other α - and β -blocking agents have included perinatal and neonatal distress.

Pediatric Use

Safety and efficacy in patients younger than 18 years of age have not been established.

Geriatric Use

Of the 765 patients with congestive heart failure randomized to Coreg in U.S. clinical trials, 31% (235) were 65 years of age or older. Of 1,869 patients receiving Coreg in congestive heart failure trials worldwide, 39% were 65 years of age or older. There were no notable differences in efficacy or the incidence of adverse events between older and younger patients.

Of the 2,065 hypertensive patients in U.S. clinical trials of efficacy or safety who were treated with Coreg (carvedilol), 21% (436) were 65 years of age or older. Of 3,722 patients receiving Coreg in hypertension clinical trials conducted worldwide, 24% were 65 years of age or older. There were no notable differences in efficacy or the incidence of adverse events between older and younger patients. With the exception of dizziness (incidence 8.8% in the elderly

vs. 6% in younger patients), there were no events for which the incidence in the elderly exceeded that in the younger population by greater than 2.0%.

Similar results were observed in a postmarketing surveillance study of 3,328 Coreg patients, of whom approximately 20% were 65 years of age or older.

ADVERSE REACTIONS

Congestive Heart Failure

Coreg has been evaluated for safety in congestive heart failure in more than 1,900 patients worldwide of whom 1,300 participated in U.S. clinical trials. Approximately 54% of the total treated population received Coreg for at least 6 months and 20% received Coreg for at least 12 months. The adverse experience profile of Coreg in congestive heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In U.S. clinical trials comparing Coreg in daily doses up to 100 mg (n=765) to placebo (n=437), 5.4% of Coreg patients discontinued for adverse experiences vs. 8.0% of placebo patients.

Table 1 shows adverse events in U.S. placebo-controlled clinical trials of congestive heart failure patients that occurred with an incidence of greater than 2% regardless of causality and were more frequent in drug-treated patients than placebo-treated patients. Median study medication exposure was 6.33 months for both Coreg (carvedilol) and placebo patients.

Table 1
Adverse Events in U.S. Placebo-Controlled Congestive Heart Failure Trials
Incidence $>2\%$, Regardless of Causality,
Withdrawal Rates due to Adverse Events

	Adverse Reactions		Withdrawals	
	Coreg (n=765) % occurrence	Placebo (n=437) % occurrence	Coreg (n=765) % withdrawals	Placebo (n=437) % withdrawals
Autonomic Nervous System				
Sweating increased	2.9	2.1	—	—
Body as a Whole				
Fatigue	23.9	27.4	0.7	0.7
Chest pain	14.4	14.2	0.1	—
Pain	8.6	7.6	—	0.2
Injury	5.9	5.5	—	—
Drug level increased	5.1	3.7	—	0.2
Edema generalized	5.1	2.5	—	—
Edema dependent	3.7	1.8	—	—
Fever	3.1	2.3	—	—
Edema legs	2.2	0.2	0.1	0.2
Cardiovascular				
Bradycardia	8.8	0.9	0.8	—
Hypotension	8.5	3.4	0.4	0.2
Syncope	3.4	2.5	0.3	0.2
Hypertension	2.9	2.5	0.1	—
AV block	2.9	0.5	—	—
Angina pectoris	2.0	1.1	—	—
aggravated	—	—	—	—
Central Nervous System				
Dizziness	32.4	19.2	0.4	—
Headache	8.1	7.1	0.3	—
Paresthesia	2.0	1.8	0.1	—
Gastrointestinal				
Diarrhea	11.8	5.9	0.3	—
Nausea	8.5	4.8	—	—
Abdominal pain	7.2	7.1	0.3	—
Vomiting	6.3	4.3	0.1	—
Hematologic				
Thrombocytopenia	2.0	0.5	0.1	—
Metabolic				
Hyperglycemia	12.2	7.8	0.1	—
Weight increase	9.7	6.9	0.1	0.5
Gout	6.3	6.2	—	—
BUN increased	6.0	4.6	0.3	0.2
NPN increased	5.8	4.5	0.3	0.2
Hypercholesterolemia	4.1	2.5	—	—
Dehydration	2.1	1.6	—	—
Hypervolemia	2.0	0.9	—	—
Musculoskeletal				
Back pain	6.9	6.6	—	—
Arthralgia	6.4	4.8	0.1	0.2
Myalgia	3.4	2.7	—	—
Resistance Mechanism				
Upper respiratory tract infection	18.3	17.6	—	—
Infection	2.2	0.9	—	—
Respiratory				
Sinusitis	5.4	4.3	—	—
Bronchitis	5.4	3.4	—	—
Pharyngitis	3.1	2.7	—	0.2
Urinary/Genital				
Urinary tract infection	3.1	2.7	—	—
Hematuria	2.9	2.1	—	—
Vision				
Vision abnormal	5.0	1.8	0.1	—

Incidence >2%, Regardless of Causality; Withdrawal Rates due to Adverse Events

In addition to the events in Table 1, asthenia, cardiac failure, flatulence, anorexia, dyspepsia, palpitation, extrasystoles, hyperkalemia, arthritis, angina pectoris, insomnia, depression, anemia, viral infection, dyspnea, coughing, respiratory disorder, rhinitis, rash, and leg cramps were also reported, but rates were equal to, or more common in, placebo-treated patients.

The following adverse events were reported more frequently with *Coreg* in U.S. placebo-controlled trials in patients with congestive heart failure:

Incidence >1% to <2%

Body as a Whole: Peripheral edema, allergy, sudden death, malaise, hypovolemia.

Cardiovascular: Fluid overload, postural hypotension.

Central and Peripheral Nervous System: Hypesthesia, vertigo.

Gastrointestinal: Melena, periodontitis.

Liver and Biliary System: SGPT increased, SGOT increased.

Metabolic and Nutritional: Hyperuricemia, hypoglycemia, hyponatremia, increased alkaline phosphatase, glycosuria.

Platelet, Bleeding and Clotting: Prothrombin decreased, purpura.

Psychiatric: Somnolence.

Reproductive, male: Impotence.

Urinary System: Abnormal renal function, albuminuria.

POSTMARKETING EXPERIENCE

The following adverse reaction has been reported in post-marketing experience: reports of aplastic anemia have been rare and received only when carvedilol was administered concomitantly with other medications associated with the event.

Hypertension

Coreg (carvedilol) has been evaluated for safety in hypertension in more than 2,193 patients in U.S. clinical trials and in 2,976 patients in international clinical trials. Approximately 36% of the total treated population received *Coreg* for at least 6 months. In general, *Coreg* was well tolerated at doses up to 50 mg daily. Most adverse events reported during *Coreg* therapy were of mild to moderate severity. In U.S. controlled clinical trials directly comparing *Coreg* monotherapy in doses up to 50 mg (n=1,142) to placebo (n=462), 4.9% of *Coreg* patients discontinued for there was no overall difference in discontinuation rates, discontinuations were more common in the carvedilol group for postural hypotension (1% vs. 0). The overall incidence of adverse events in U.S. placebo-controlled trials was found to increase with increasing dose of *Coreg*. For individual adverse events this could only be distinguished for dizziness, which increased in frequency from 2% to 5% as total daily dose increased from 6.25 mg to 50 mg. Table 2 shows adverse events in U.S. placebo-controlled clinical trials for hypertension that occurred with an incidence of greater than 1% regardless of causality, and that were more frequent in drug-treated patients than placebo-treated patients.

Table 2

**Adverse Events in U.S. Placebo-Controlled Hypertension Trials
Incidence ≥1%, Regardless of Causality;
Withdrawal Rates due to Adverse Events**

Adverse Reactions	Coreg (n=1,142)		Placebo (n=462)	
	% occurrence	% occurrence	% withdrawals	% withdrawals
Body as a Whole				
Fatigue	4.3	3.9	0.3	0.2
Injury	2.9	2.6	0.1	—
Cardiovascular				
Bradycardia	2.1	0.2	0.4	—
Postural hypotension	1.8	—	1.0	—
Dependent edema	1.7	1.5	0.1	0.4
Peripheral edema	1.4	0.4	0.2	—
Central Nervous System				
Dizziness	6.2	5.4	0.4	1.3
Insomnia	1.6	0.6	—	0.2
Somnolence	1.8	1.5	—	—
Gastrointestinal				
Abdominal pain	1.4	1.3	0.1	—
Diarrhea	2.2	1.3	0.1	—
Hematologic				
Thrombocytopenia	1.1	0.2	—	—
Metabolic				
Hypertiglyceridemia	1.2	0.2	—	—

Musculoskeletal	Back pain	2.3	1.5	0.1	—
Resistance Mechanism					
Viral infection	1.8	1.3	—	—	
Respiratory					
Rhinitis	2.1	1.9	—	—	
Pharyngitis	1.5	0.6	—	—	
Dyspnea	1.4	0.9	0.4	0.2	
Urinary/renal					
Urinary tract infection	1.6	0.6	—	—	

In addition to the events in Table 2, chest pain, dyspepsia, headache, nausea, pain, sinusitis and upper respiratory tract infection were also reported, but rates were at least as great in placebo-treated patients.

The following adverse events were reported as possibly or probably related in worldwide open or controlled trials with *Coreg* (carvedilol) in patients with hypertension or congestive heart failure.

Incidence >0.1% to ≤1%

Cardiovascular: Peripheral ischemia, tachycardia.

Central and Peripheral Nervous System: Hypokinesia.

Gastrointestinal: Bilirubinemia, increased hepatic enzymes (0.2% of hypertension patients and 0.4% of congestive heart failure patients were discontinued from therapy because of increases in hepatic enzymes; see WARNINGS, Hepatic Injury).

General: Substernal chest pain, edema.

Psychiatric: Nervousness, sleep disorder, aggravated depression, impaired concentration, abnormal thinking, paranoia, emotional lability.

Respiratory System: Asthma (see CONTRAINDICATIONS).

Reproductive: Male: decreased libido.

Skin and Appendages: Pruritus, rash erythematous, rash maculopapular, rash psoriasisiform, photosensitivity reaction.

Special Senses: Tinnitus.

Urinary System: Micturition frequency.

Autonomic Nervous System: Dry mouth, sweating increased.

Metabolic and Nutritional: Hypokalemia, diabetes mellitus, hypertiglyceridemia.

Hematologic: Anemia, leukopenia.

The following events were reported in ≤0.1% of patients and are potentially important: complete AV block, bundle branch block, myocardial ischemia, cerebrovascular disorder, convulsions, migraine, neuralgia, paresis, anaphylactoid reaction, alopecia, exfoliative dermatitis, amnesia, GI hemorrhage, bronchospasm, pulmonary edema, decreased hearing, respiratory alkalosis, increased BUN, decreased HDL, pancytopenia and atypical lymphocytes. Other adverse events occurred sporadically in single patients and cannot be distinguished from concurrent disease states or medications.

Coreg therapy has not been associated with clinically significant changes in routine laboratory tests in hypertensive patients. No clinically relevant changes were noted in serum potassium, fasting serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen or creatinine.

OVERDOSAGE

The acute oral LD₅₀ doses in male and female mice and male and female rats are over 8000 mg/kg.

Overdosage may cause severe hypotension, bradycardia, cardiac insufficiency, cardiogenic shock and cardiac arrest. Respiratory problems, bronchospasms, vomiting, lapses of consciousness and generalized seizures may also occur.

The patient should be placed in a supine position and, where necessary, kept under observation and treated under intensive-care conditions. Gastric lavage or pharmacologically induced emesis may be used shortly after ingestion. The following agents may be administered: for excessive bradycardia: atropine, 2 mg IV.

to support cardiovascular function: glucagon, 5 to 10 mg IV rapidly over 30 seconds, followed by a continuous infusion of 5 mg/hour; sympathomimetics (dobutamine, isoprenaline, adrenaline) at doses according to body weight and effect.

If peripheral vasodilation dominates, it may be necessary to administer adrenaline or noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant bradycardia, pacemaker therapy should be performed. For bronchospasm, β-sympathomimetics (as aerosol or IV) or aminophylline IV should be given. In the event of seizures, slow IV injection of diazepam or clonazepam is recommended.

NOTE: In the event of severe intoxication where there are symptoms of shock, treatment with antidotes must be

continued for a sufficiently long period of time consistent with the 7- to 10-hour half-life of carvedilol.

Cases of overdosage with *Coreg* alone or in combination with other drugs have been reported. Quantities ingested in some cases exceeded 1000 milligrams. Symptoms experienced included low blood pressure and heart rate. Standard supportive treatment was provided and individuals recovered.

DOSAGE AND ADMINISTRATION

Congestive Heart Failure

DOSAGE MUST BE INDIVIDUALIZED AND CLOSELY MONITORED BY A PHYSICIAN DURING UP-TITRATION.

Prior to initiation of *Coreg*, the dosing of digitalis, diuretics and ACE inhibitors (if used) should be stabilized. The recommended starting dose of *Coreg* is 3.125 mg twice daily for two weeks. If this dose is tolerated, it can then be increased to 6.25 mg twice daily. Dosing should then be doubled every 2 weeks to the highest level tolerated by the patient. At initiation of each new dose, patients should be observed for signs of dizziness or light-headedness for one hour. The maximum recommended dose is 25 mg twice daily in patients weighing less than 85 kg, 15 mg and 50 mg twice daily in patients weighing more than 85 kg. *Coreg* (carvedilol) should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

Before each dose increase the patient should be seen in the office and evaluated for symptoms of worsening heart failure, vasodilation (dizziness, light-headedness, symptomatic hypotension) or bradycardia, in order to determine tolerability of *Coreg*. Transient worsening of heart failure may be treated with increased doses of diuretics although occasionally it is necessary to lower the dose of *Coreg* or temporarily discontinue it. Symptoms of vasodilation often respond to a reduction in the dose of diuretics or ACE inhibitor. If these changes do not relieve symptoms, the dose of *Coreg* may be decreased. The dose of *Coreg* should not be increased until symptoms of worsening heart failure or vasodilation have been stabilized. Initial difficulty with titration should not preclude later attempts to introduce *Coreg*. If congestive heart failure patients experience bradycardia (pulse rate below 55 beats/min.), the dose of *Coreg* should be reduced.

Hypertension

DOSAGE MUST BE INDIVIDUALIZED. The recommended starting dose of *Coreg* is 6.25 mg twice daily. If this dose is tolerated, using standing systolic pressure measured about 1 hour after dosing as a guide, the dose should be maintained for 7 to 14 days, and then increased to 12.5 mg twice daily if needed, based on trough blood pressure, again using standing systolic pressure one hour after dosing as a guide for tolerance. This dose should also be maintained for 7 to 14 days and can then be adjusted upward to 25 mg twice daily if tolerated and needed. The full antihypertensive effect of *Coreg* is seen within 7 to 14 days. Total daily dose should not exceed 50 mg. *Coreg* should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

Addition of a diuretic to *Coreg*, or *Coreg* to a diuretic can be expected to produce additive effects and exaggerate the orthostatic component of *Coreg* action.

Coreg (carvedilol) should not be given to patients with severe hepatic impairment (see CONTRAINDICATIONS).

HOW SUPPLIED

Tablets: White, oval, film-coated tablets: 3.125 mg engraved with 39 and SB, in bottles of 100; 6.25 mg engraved with 4140 and SB, in bottles of 100; 12.5 mg engraved with 4141 and SB, in bottles of 100; 25 mg engraved with 4142 and SB, in bottles of 100. The 6.25 mg, 12.5 mg and 25 mg tablets are Titab[®] tablets. Store below 30°C (86°F). Protect from moisture. Dispense in a tight, light-resistant container.

3.125 mg 100's: NDC 0007-4139-20

6.25 mg 100's: NDC 0007-4140-20

12.5 mg 100's: NDC 0007-4141-20

25 mg 100's: NDC 0007-4142-20

Coreg is a registered trademark.

Coreg is copromoted by SmithKline Beecham Pharmaceuticals and Roche Laboratories Inc.

DATE OF ISSUANCE MAR. 1999

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Manufactured and distributed by

SmithKline Beecham Pharmaceuticals

Philadelphia, PA 19101

CO:L5A

R_x only

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20297/S004

ADMINISTRATIVE DOCUMENTS

CPMS Review of Final Printed Labeling
NDA 20-297/S-004

Sponsor Name: **SmithKline Beecham Pharmaceuticals**
Drug Product Name: **Coreg (carvedilol) Tablets**
Date of Submission: May 6, 1999
Date of Review: August 18, 1999

In a letter dated December 8, 1998, FDA requested that the firm add a discussion of the interaction between carvedilol and cyclosporin to the **CLINICAL PHARMACOLOGY/Pharmacokinetic Drug-Drug Interactions** subsection of the labeling for Coreg. This request was based on an abstract of a study that the firm submitted in their November 13, 1998 annual report. The study was entitled, "Elevation of cyclosporin A blood levels during carvedilol treatment in renal transplant patients" by Kaijser, M., *et al*, Clin Transplant Dec 1997, 11(6) p577-81.

In response to this request the firm submitted this **Special Supplement – Changes Being Effectuated**. The supplemental application provides for final printed labeling revised by adding a new section to the Precautions/Drug Interactions section immediately prior to the section on Digoxin. The new section follows:

Cyclosporin: Modest increases in mean trough cyclosporin concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30% of patients, the dose of cyclosporin had to be reduced in order to maintain cyclosporin concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclosporin was reduced about 20% in these patients. Due to wide interindividual variability in the dose adjustment required, it is recommended that cyclosporin concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporin be adjusted as appropriate.

Also added to the **How Supplied** section was the statement, "Rx only" as well as minor editorial changes.

The medical officer, Dr. Norman Stockbridge, stated that this change is acceptable. Further review of the labeling indicates that except for the new section above, the "Rx only" statement and minor editorial changes, no other changes have been made since the last labeling was approved on July 28, 1998. This supplemental application can be approved. An approval letter will be prepared for Dr. Lipicky's signature.

NS
Natalia A. Morgenstern
Chief, Project Management Staff

Cc: Orig NDA
HFD-110/ZMcDonald
HFD-110/Blount
HF-2/MedWatch

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20297/S004

CORRESPONDENCE

SB
SmithKline Beecham
Pharmaceuticals

ORIGINAL

May 6, 1999

NDA 20-297
COREG® (carvedilol) Tablets

NDA NO. 20-297 REF. NO. 004
NDA SUPPL FOR SLR

Raymond J. Lipicky, M.D., Director
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products (HFD-110)
Document Control Room
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20857

Special Supplement – Changes Being Effected



Dear Dr. Lipicky:

Reference is made to our approved New Drug Application for Coreg® (carvedilol) Tablets.

Additional reference is also made to a request from the Division to include a section in the approved Prescribing Information regarding a potential for increased cyclosporin levels in renal transplant patients receiving carvedilol. In a recent conversation, the following wording regarding cyclosporin was judged satisfactory: "*Cyclosporin*: Modest increases in mean trough cyclosporin concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30% of patients, the dose of cyclosporin had to be reduced in order to maintain cyclosporin concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclosporin was reduced about 20% in these patients. Due to wide interindividual variability in the dose adjustment required, it is recommended that cyclosporin concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporin be adjusted as appropriate." The new section appears in the Precautions/Drug Interactions section of the labeling immediately prior to the section on Digoxin.

Enclosed are twelve copies of final printed labeling (CO:L5A and CO:L5B) for Coreg® containing the aforementioned wording. The first commercial use of this final printed labeling took place on May 4, 1999.

Raymond J. Lipicky, M.D., Director

May 6, 1999

Page 2

If you have questions regarding this supplement, please contact me by telephone at (610) 917-5368 or by facsimile at (610) 917-4708.

Sincerely,



Catherine K. Clark

Director

U.S. Regulatory Affairs